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Birth order and childhood type 1 diabetes risk: a pooled analysis of 31 observational studies

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Background The incidence rates of childhood onset type 1 diabetes are almost universally increasing across the globe but the aetiology of the disease remains largely unknown. We investigated whether birth order is associated with the risk of childhood diabetes by performing a pooled analysis of previous studies.

Methods Relevant studies published before January 2010 were identified from MEDLINE, Web of Science and EMBASE. Authors of studies provided individual patient data or conducted pre-specified analyses. Meta-analysis techniques were used to derive combined odds ratios (ORs), before and after adjustment for confounders, and investigate heterogeneity.

Results Data were available for 6 cohort and 25 case–control studies, including 11 955 cases of type 1 diabetes. Overall, there was no evidence of an association prior to adjustment for confounders.

After adjustment for maternal age at birth and other confounders, a reduction in the risk of diabetes in second- or later born children became apparent [fully adjusted OR = 0.90 95% confidence interval (CI) 0.83–0.98; $P = 0.02$] but this association varied markedly between studies ($I^2 = 67\%$). An a priori subgroup analysis showed that the association was stronger and more consistent in children <5 years of age ($n = 25$ studies, maternal age adjusted OR = 0.84 95% CI 0.75, 0.93; $I^2 = 23\%$).

Conclusion Although the association varied between studies, there was some evidence of a lower risk of childhood onset type 1 diabetes with increasing birth order, particularly in children aged <5 years. This finding could reflect increased exposure to infections in early life in later born children.

Keywords Diabetes mellitus, type 1, epidemiology, birth order, meta-analysis

Introduction

The incidence of childhood onset type 1 diabetes is increasing by ~50% every 10 years.[1,2] The pace of this increase, within genetically stable populations, suggests the role of environmental exposures, but these exposures remain largely unidentified. More recently, researchers have speculated that the hygiene hypothesis,[3] which suggests that the immune system requires stimulation by infection and other immune challenges to achieve a mature and balanced repertoire of responses, could explain this increase. Partly to examine this hypothesis, many studies have investigated the association between birth order and childhood onset type 1 diabetes. However, the findings of these studies are difficult to interpret due to the large number of studies conducted, the differing sizes (and powers) of these studies and the inconsistent presentation of birth order results. Also, many studies do not report results adjusted for important confounders such as maternal age, which is associated with both birth order and childhood diabetes risk and therefore could distort any birth order association.[4]

The aim of this study was to perform a systematic review and meta-analysis to assess the evidence of an association between birth order and type 1 diabetes, and to adjust for potential confounding by relevant factors such as maternal age, breastfeeding and maternal diabetes.[5–7]

Methods

Literature search

The main literature search was conducted using MEDLINE, through OVID ONLINE, and the strategy was: ('Birth Order' or birth order or 'Parity' or parity or first born) and ['Diabetes Mellitus, Type 1' or (diabetes and Type 1) or IDDM] using the terms in inverted commas as MEDLINE subject heading key words. Similar searches were conducted on Web of Science and EMBASE. Finally, to identify studies that investigated birth order along with other risk factors, a more general search was conducted on MEDLINE using: ['Diabetes Mellitus, Type 1' and ('Case-Control Studies' or 'Cohort Studies')]. The searches were limited to studies on humans published before January 2010. Abstracts were screened independently by two investigators (C.R.C. and C.C.P.) to establish if the studies were likely to provide relevant data based on the following inclusion criteria: (i) they identified a group with type 1 diabetes and a group without type 1 diabetes; and (ii) they recorded birth order in these groups. Studies were excluded if they contained fewer than 100 cases (because adjustments for confounders may not perform well in these studies) or if they were family based (because in such studies every only child must be a case, leading to a distorted association between birth order and diabetes). Citations generated from the more general MEDLINE search were initially screened to remove obviously irrelevant articles. Finally, the reference lists of all pertinent articles were hand searched and the corresponding author of each included article was asked if they were aware of any additional studies.

An author from each included study was contacted because categorizations (and adjustments) differed in published reports and some authors who recorded birth order did not present birth order findings. These authors were invited to provide raw data sets, or estimates from pre-specified analyses, for the association between birth order and type 1 diabetes before and after adjustments for maternal age (if available) and other potential confounders (if available).

Details of included studies (reported in Table 1) were extracted by one reviewer (C.R.C.) and agreed with the study author.

Table 1 Characteristics of included studies investigating the association between birth order and type 1 diabetes, ordered by publication date

First author, year (reference)	Design	Country	Type 1 diabetes				Controls			Available confounders[b]					
			Ascertainment method (year cases diagnosed)	Age at diagnosis (years)	n[a]	Resp. rate (%)	Source (matching criteria)	n[a]	Resp. rate (%)	MA	BW	GA	MD	CS	BF[f] (months)
Glatthaar, 1988[13]	C–C	Australia	School Survey (1984)	0–14	157	99	School survey (age, sex)	623	?						
Patterson, 1994[16]	C–C	Scotland	Hospital Admission/Childhood Diabetes Register (1976–88)	0–14	271	100	Maternal discharge records (age, sex, area)	1355	100	✓	✓	✓	✓	✓	
Bock, 1994[17]	C–C	Denmark	Hospital admission from National Patient Registry (1978–89)	<16	837	98	Birth registry (age, sex)	837	NA						
Wadsworth, 1997[18]	C–C	UK	British Paediatric Association Surveillance Unit (1992)	0–5	216	89	Health Authority Immunization Register	318	70	✓	✓		✓		✓(4)
Gimeno, 1997[19]	C–C	Brazil	Diabetes association/hospital admission (1995)	0–19	345	91	Unclear (neighbourhood, sex, age)[d]	333	100	✓	✓		✓		✓(3)
McKinney, 1999[20]	C–C	England	Yorkshire Childhood Diabetes Register (1993–94)	0–15	220	94	General practitioner's records (age, sex)	423	82	✓	✓	✓	✓	✓	✓(any)
Rami, 1999[21]	C–C	Austria	Vienna Type 1 diabetes register (1989–94)	0–14	104	86	Schools (age, sex)	373	80	✓	✓	✓	✓[c]	✓	✓(any)
	C–C	Bulgaria	W. Bulgaria Type 1 diabetes register (1991–94)	0–14	125	73	Schools and policlinics (age)	440	79	✓	✓	✓	✓[c]	✓	✓(any)
	C–C	Latvia	Latvian Type 1 diabetes register (1989–94)	0–14	140	99	Population register (age)	301	79	✓	✓	✓	✓[c]	✓	✓(any)
Eurodiab, 1999[6]	C–C	Lithuania	Lithuanian Type 1 diabetes register (1989–94)	0–14	111	94	Policlinics (age)	266	73	✓	✓	✓	✓[c]	✓	✓(any)
	C–C	Luxembourg	Luxembourg Type 1 diabetes register (1989–95)	0–14	58	100	Pre-schools and schools (age)	172	95	✓	✓	✓	✓[c]	✓	✓(any)
	C–C	Romania	Bucharest Type 1 diabetes register (1989–94)	0–14	81	74	Pre-schools and schools (age)	277	81	✓	✓	✓	✓[c]	✓	✓(any)
Stene, 2001[5]	Cohort	Norway	Norwegian Childhood Diabetes Registry (1989–98)	0–14	1810	100[e]	Norwegian medical birth registry	1 382 602	NA	✓	✓	✓	✓	✓	
Stene, 2004[23]	C–C	Norway	Norwegian Childhood Diabetes Registry (1998–2000)	0–14	340	73	Norwegian population registry	1626	56	✓	✓	✓	✓[c]	✓	✓(3)
Sadauskaite–Kuehne, 2004[7]	C–C	Sweden	S.E. Sweden Type 1 diabetes register (1995–2000)	0–15	516	100	Population register	1084	73	✓	✓	✓	✓[c]		✓(3)
	C–C	Lithuania	Lithuanian Type 1 diabetes register (1996–2000)	0–15	286	100	Outpatient clinic[d]	807	95	✓	✓	✓	✓[c]		✓(3)
Sumnik, 2004[24]	C–C	Czech republic	Czech Republic Type 1 diabetes Registry (1995–2000)	0–15	640	79	National Birth Registry (age)	32 000	100	✓					
Marshall, 2004[25]	C–C	England	Morecombe Bay/E. Lancashire diabetes clinics (1998)	0–15	196	83	Health Authorities (sex, birth date)	381	53	✓	✓	✓	✓[c]		✓(any)

(continued)

Table 1 Continued

First author, year (reference)	Design	Country	Type 1 diabetes: Ascertainment method (year cases diagnosed)	Age at diagnosis (years)	n[a]	Resp. rate (%)	Controls: Source (matching criteria)	n[a]	Resp. rate (%)	Available confounders[b]: MA	BW	GA	MD	CS	BF[f] (months)
Cardwell, 2005[11]	Cohort	Northern Ireland	Northern Ireland Type 1 diabetes register (1971–2001)	0–14	913	92[e]	Northern Ireland Child Health register	439 647	NA	✓	✓	✓	✓	✓	✓(any)
Sipetic, 2005[26]	C–C	Serbia	Belgrade Hospital admission (1994–97)	0–16	105	91	Hospital outpatients with skin disease[d] (age, sex, area)	210	100	✓	✓	✓	✓[c]	✓	✓(4)
Svensson, 2005[27]	C–C	Denmark	Danish register of childhood diabetes (1996–99)	0–14	477	81	Danish population register (age, sex)	679	48	✓	✓	✓	✓	✓	✓(4)
Bottini, 2005[29]	C–C	Sardinia	Hospital diagnosis	?	187	?	Consecutive births in northern Sardinia	5460	?						
Radon, 2005[30]	C–C	Germany	Paediatric referral centre admission	6–16	242	91	Surgery patients (hospital)[d]	224	91						
Polanska, 2006[31]	C–C	Poland	Upper Silesia Diabets Register (1989–96)	0–14	397	87	Central Bureau for Statistics	994 460	100	✓	✓				
Wei, 2006[32]	C–C	Taiwan	School-based urine screening programme and questionnaire (1992–97)	0–18	277	87	Randomly selected negatives from screening program	533	88	✓	✓	✓	✓		✓(3)
Tenconi, 2007[33]	C–C	Italy	Pavia Type 1 diabetes register (1988–2000)	0–19	98	85	Hospital (age, sex, week)[d]	194	?	✓					
Haynes, 2007[34]	Cohort	Australia	W. Australian Children's Diabetes Register (1980–2002)	0–14	920	99[e]	Western Australia Midwives' Notification System	~557 707	NA	✓	✓	✓	✓		
Ievins, 2007[35]	Cohort	England	Hospital admission [ICD diabetes code] (1963–99)	0–14	410	?	Oxfordshire/West Berkshire maternity records	266 665	NA	✓	✓	✓	✓	✓	✓(any)
Rosenbauer, 2008[36]	C–C	Germany	Nationwide hospital- based surveillance (1992–95)	0–4	760	71	Local registration offices (age, sex, area)	1871	43	✓	✓		✓[c]		✓(4)
Waldhoer, 2008[37]	Cohort	Austria	Austrian diabetes register (89–05)	0–5	444	85[e]	Birth certificate registry	1 435 385	NA	✓	✓	✓			
Algert, 2009[38]	Cohort	Australia	Hospital admission [ICD diabetes code] (2000–05)	0–6	272	93	Midwives' database	502 040	NA	✓	✓	✓	✓[c]	✓	

BF, breastfeeding (in months); BW, birth weight; C–C, case–control; CS, caesarean section; GA, gestational age; MA, maternal age; MD, maternal diabetes; NA, not available; ICD, International Classification of Diseases.

[a]Number included in analysis of birth order.

[b]Tick denotes data recorded in study and available for analysis.

[c]Maternal type 1 diabetes used in analyses.

[d]Not randomly selected and population-based.

[e]Percentage of cases identified in cohort.

[f]Duration of breastfeeding used in adjusted analysis shown in parentheses.

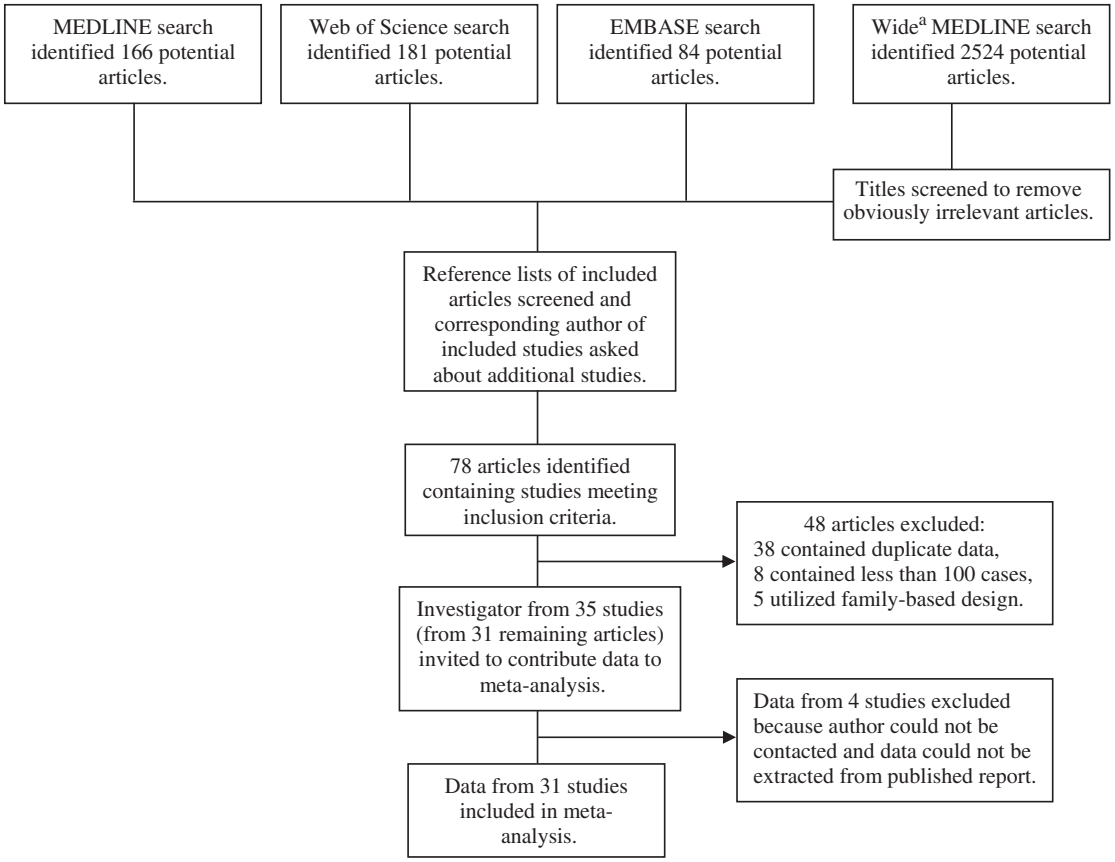

Figure 1 Flow chart of search results. [a]Wide search included terms for type 1 diabetes and case–control or cohort studies, whilst other searches included search terms for birth order and type 1 diabetes (see Methods for further details)

Statistical analysis

Odds ratios (ORs) and standard errors (SEs) were calculated for the association between categories of birth order and childhood type 1 diabetes for each study. Adjustments for confounders were conducted using regression models consistent with the study design, before random-effects models were used to calculate pooled ORs.[8] Unconditional and conditional logistic regression was used to calculate the ORs and SEs for the unmatched and matched case–control studies, respectively. In cohort studies with varying length of participant follow-up, Poisson regression was used to estimate rate ratios and their SEs as measures of association (which should be approximately equal to ORs for a rare disease such as type 1 diabetes).[9] A year of birth term was added to Poisson regression models to adjust the rate ratios for any differences in year of birth between cases and controls resulting from this study design. Tests for heterogeneity were conducted and the I^2 statistic was calculated to quantify the degree of heterogeneity between studies. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study ORs against the standard error of the logarithm of the ORs.

Meta regression techniques[10] were used to investigate whether any association between birth order and diabetes varied by year of publication or response rates in cases and controls. Subgroup analyses were conducted subdividing studies by type and including only studies with a reduced risk of bias (excluding case–control studies with non-population-based or non-randomly selected controls or any study with a response rate of <80% in either the cases or controls). An a priori subgroup analysis was conducted by age at diagnosis of diabetes (as a previous study suggested that the birth order association was only apparent in children aged <5 years)[11] and pooled estimates were compared by age at onset using standard tests for heterogeneity.[12]

All statistical analyses were performed using STATA 9.0 (Stata, College Station, TX, USA).

Results

Search results

A flow chart describing the results of the literature searches is shown in Figure 1. The searches identified 78 relevant articles (a full list is available from the

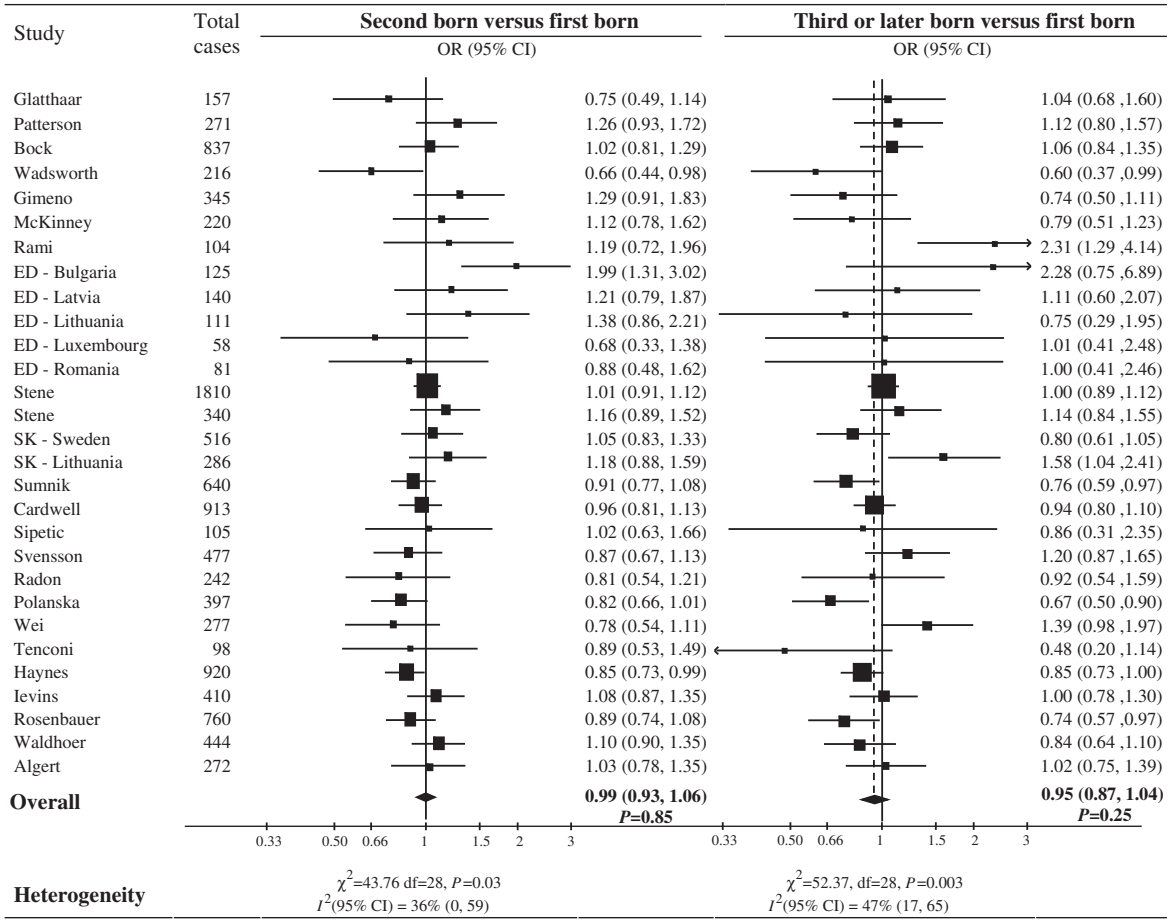

Figure 2 Meta-analysis of studies of birth order and type 1 diabetes using the random effects model, studies ordered by publication date. ED, Eurodiab; SK, Sadauskaite-Kuehne; CI, confidence interval; df, degrees of freedom

authors). Of these, 48 were excluded: 35 contained duplicate or overlapping information, 8 contained information on fewer than 100 cases and 5 utilized family-based designs.

The remaining 30 articles[5–7,11,13–38] contained information from 35 independent studies, as information from five centres was taken from 1 article[6] and information from two centres was taken from another.[7] An investigator from each of the 35 studies was invited to provide raw data (or estimates from pre-specified analyses). Full datasets were obtained from 22 studies,[6,7,11,16,18–21,24,26,27,31–35,37] in eight studies authors provided estimates from pre-specified analyses,[5,13,17,23,25,30,36,38] in one study an estimate was extracted directly from the published report[29] (as the author could not be contacted) and in four studies[14,15,22,28] data were not available. In 29 studies data were available for birth order in three categories (first-born children, second-born children and third- or later born children) allowing an investigation of the shape of any association, whilst in 2 studies[25,29] only two categories were available (first born, second or later born).

Table 1 contains the characteristics of the 31 studies, containing 11 955 cases of type 1 diabetes, included in the analysis. These studies were published between 1988 and 2009. They contain 6 cohort studies and 25 case–control studies and were predominately conducted in Europe, apart from 3 studies from Australia and 1 each from Taiwan and Brazil.

Overall findings

Overall (in 29 studies), there was little evidence of a difference in the risk of type 1 diabetes in second-born children [OR = 0.99 95% confidence interval (CI) 0.93, 1.06] or third- or later born children (OR = 0.95 95% CI 0.87, 1.04) compared with first-born children and there was marked heterogeneity between studies (Figure 2 and Table 2).

After adjustment for maternal age at birth (in 26 studies) there was some evidence of a reduction in diabetes risk in second- born children of 5% (OR = 0.95 95% CI 0.88, 1.04) and a more marked reduction of in the third- or later born children of 14% (OR = 0.86 95% CI 0.76, 0.97), compared with

Table 2 Meta-analyses of 31 studies investigating the association between birth order and type 1 diabetes (including 11 955 cases) before and after adjustments for recorded confounders

Analysis	Birth order	Number of studies	Number of cases	Combined OR (95% CI)	*P*	Heterogeneity	
						χ^2 (*P*)	I^2
Unadjusted	First born		5261	1.00 (Ref. Cat.)			
	Second born	29	4142	0.99 (0.93–1.06)	0.85	43.76 (0.03)	36
	Third or later born	29	2364	0.95 (0.87–1.04)	0.25	52.37 (0.003)	47
	Second or later born	31	6690	0.96 (0.90–1.03)	0.25	62.23 (<0.001)	52
Adjusted for maternal age[a]	First born		4625	1.00 (Ref. Cat.)			
	Second born	26	3545	0.95 (0.88–1.04)	0.25	55.30 (<0.001)	55
	Third or later born	26	2141	0.86 (0.76–0.97)	0.02	71.56 (<0.001)	65
	Second or later born	27	5782	0.92 (0.85–1.01)	0.07	70.63 (<0.001)	65
Adjusted for all available confounders as shown in Table 1	First born		5036	1.00 (Ref. Cat.)			
	Second born	29	3937	0.93 (0.85–1.02)	0.12	68.25 (<0.001)	59
	Third or later born	29	2208	0.87 (0.77–0.98)	0.02	78.44 (<0.001)	64
	Second or later born	31	6329	0.90 (0.83–0.98)	0.02	91.27 (<0.001)	67
In cohort studies (adjusted for maternal age[a])	First born		1921	1.00 (Ref. Cat.)			
	Second born	6	1640	0.94 (0.86–1.03)	0.21	8.12 (0.15)	38
	Third or later born	6	1206	0.84 (0.77–0.92)	<0.001	5.71 (0.34)	12
	Second or later born	6	2846	0.91 (0.83–1.00)	0.049	9.97 (0.08)	50
In case–control studies (adjusted for maternal age[a])	First born		2704	1.00 (Ref. Cat.)			
	Second born	23	1905	0.96 (0.85–1.09)	0.51	47.08 (<0.001)	60
	Third or later born	23	935	0.87 (0.71–1.07)	0.81	65.81 (<0.001)	71
	Second or later born	25	2936	0.93 (0.82–1.06)	0.29	60.60 (<0.001)	67
In studies with a low risk of bias (adjusted for maternal age[a])	First born		2302	1.00 (Ref. Cat.)			
	Second born	11	1935	0.90 (0.81–0.99)	0.04	19.09 (0.04)	48
	Third or later born	11	1427	0.82 (0.70–0.96)	0.01	31.12 (0.001)	68
	Second or later born	11	3362	0.87 (0.79–0.97)	0.01	24.58 (0.006)	59

[a]Where available see Table 1.

the first- born children (Figure 3 and Table 2). However, there was marked heterogeneity between studies for these associations ($I^2 = 55$ and 65%, respectively). These estimates were little altered after further adjustment for all available confounders [included birth weight, gestational age, caesarean section delivery, breastfeeding and maternal diabetes (see Table 1 for availability)].

Funnel plots of the association between birth order and odds of type 1 diabetes were investigated (Supplementary Figure 1 available as supplementary data at *IJE* online) and roughly conformed to the expected funnel shape providing little evidence of asymmetry, which could signify publication bias.

Sensitivity analysis and investigation of heterogeneity

The main associations after adjustment for maternal age at birth were similar in cohort and case–control studies (Table 2), showing a reduction in type 1 diabetes risk in third- or later born children compared with first-born children (adjusted OR = 0.84 95% CI 0.77, 0.92 and 0.87 95% CI 0.71, 1.07, respectively). There was less evidence of the heterogeneity of this association in the cohort studies ($I^2 = 12\%$) compared with the case–control studies ($I^2 = 71\%$).

Table 2 also shows a separate analysis including only studies with a low risk of bias (excluding case–control studies with non-population-based or non-randomly selected controls and excluding studies with a response rate of <80% in either the case group or control group). Overall, in the 11 studies with a low risk of bias, there was a slightly more marked reduction in diabetes risk in second-born children (OR = 0.90 95% CI 0.81, 0.99; $P = 0.04$) and in third- or later born children (OR = 0.82 95% CI 0.70, 0.96; $P = 0.01$) compared with first-born children but the heterogeneity remained ($I^2 = 48$ and 68%, respectively).

Further analyses were conducted to attempt to identify the source of the heterogeneity. Meta regression

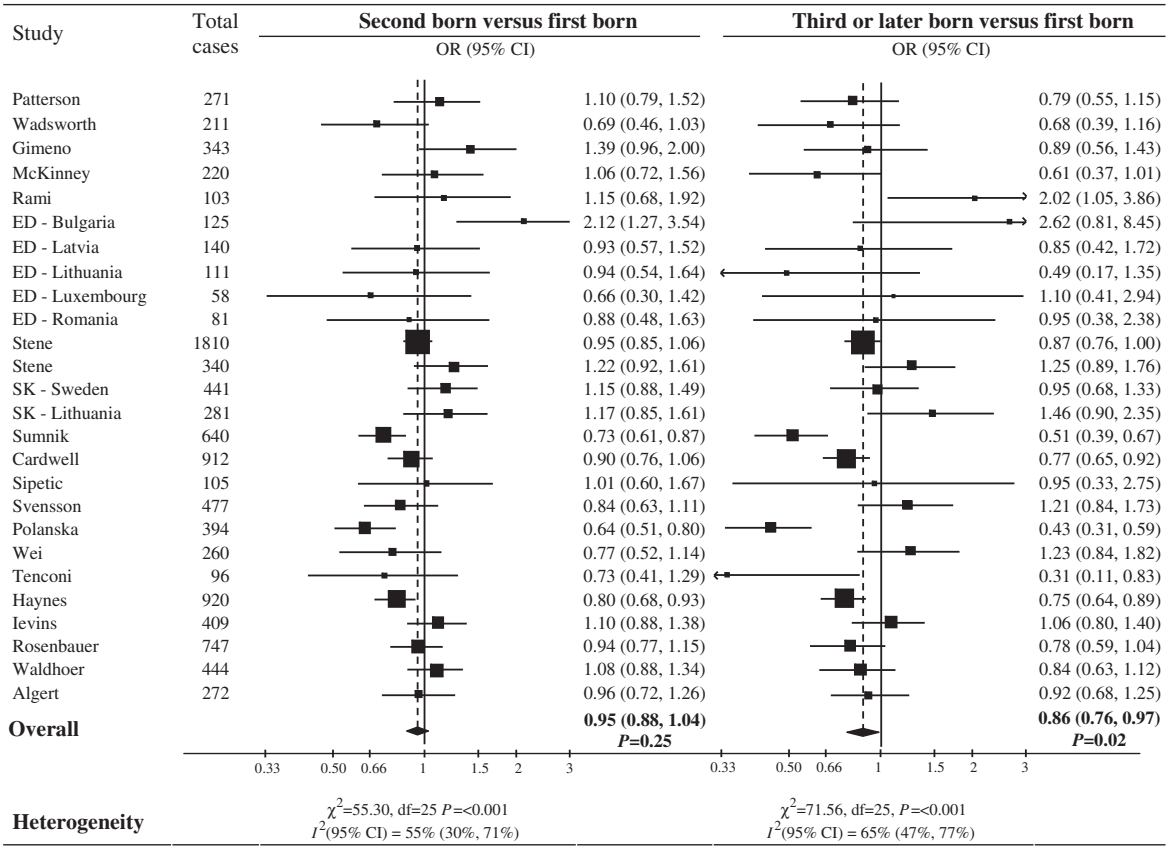

Figure 3 Meta-analysis of studies of the association between birth order and type 1 diabetes after adjustment for maternal age using the random effects model, studies ordered by publication date. ED, Eurodiab; SK, Sadauskaite-Kuehne; df, degrees of freedom

was used to investigate whether the OR in second- or later born children compared with first-born children (after adjustment for maternal age) was associated with other study characteristics. However, there was little evidence that this OR was correlated with control response rate (per 10% increase the adjusted OR reduced by 2% 95% CI –6, +3; *P* from meta-regression = 0.43), or case response rate (per 10% increase the adjusted OR reduced by 2% 95% CI –12, +9; P from meta-regression = 0.73) or year of study (per decade increase the adjusted OR reduced by 10% 95% CI –29, +14; *P* from meta-regression = 0.38).

Association by age group

The association between birth order and early diagnosed diabetes (i.e. <5 years of age) in 25 studies (including 3288 cases) is shown in Table 3. Overall, in children aged <5 years there was some evidence of a reduction in the risk of type 1 diabetes in second-born children (maternal age adjusted OR = 0.90 95% CI 0.81, 0.99; $P = 0.04$) and third- or later born children (maternal age adjusted OR = 0.78 95% CI 0.68, 0.99; $P < 0.001$) and there was little evidence of heterogeneity between studies ($I^2 = 9$ and 16%, respectively. Table 3 also shows that these associations were similar in cohort studies, case–control studies and in studies with a low risk of bias.

In contrast, there was little evidence of any association between birth order and childhood diabetes diagnosed between 5 and 15 years based upon 22 studies (including 5935 cases). Specifically, there was no evidence of an association in second-born children (maternal age adjusted OR = 1.04 95% CI 0.92, 1.18; $P = 0.45$) or third- or later born children compared with first-born children (maternal age adjusted OR = 0.98 95% CI 0.81, 1.18; $P = 0.88$). There was marked heterogeneity for both associations ($I^2 = 58$ and 68%, respectively).

Formal comparisons of the association by age at diagnosis revealed evidence that the OR per category increase in birth order was different in the <5s compared with the >5s (OR = 0.89 95% CI 0.83, 0.95 and OR = 1.00 95% CI 0.91, 1.10, respectively; *P* for interaction = 0.04). Additional analysis revealed little evidence of any difference in diabetes risk in later born children diagnosed in the 5–10 age group (OR = 1.00, 95% CI 0.82, 1.21) or diagnosed in the 10–15 age group (OR = 1.08, 95% CI 0.90, 1.29) in 19 studies with available data.

Table 3 Meta-analyses of studies investigating the association between birth order and type 1 diabetes in children <5 years of age (including 3288 cases) after adjustments for maternal age

Analysis	Birth order	Number of studies	Number of cases	Combined OR (95% CI)	*P*	Heterogeneity	
						χ^2 (*P*)	I^2
Unadjusted	First born		1590	1.00 (Ref. Cat.)			
	Second born	24	1084	0.92 (0.84–1.01)	0.07	23.64 (0.42)	3
	Third or later born	24	575	0.84 (0.75–0.93)	0.001	19.92 (0.65)	0
	Second or later born	25	1698	0.88 (0.81–0.96)	0.003	26.31 (0.34)	9
Adjusted for maternal age[a]	First born		1572	1.00 (Ref. Cat.)			
	Second born	24	1076	0.90 (0.81–0.99)	0.04	25.17 (0.34)	9
	Third or later born	24	570	0.78 (0.68–0.89)	<0.001	27.31 (0.24)	16
	Second or later born	25	1685	0.84 (0.75–0.93)	0.001	30.52 (0.17)	21
In cohort studies (adjusted for maternal age[a])	First born		570	1.00 (Ref. Cat.)			
	Second born	5	468	0.92 (0.72–1.17)	0.50	13.07 (0.01)	69
	Third or later born	5	301	0.82 (0.62–1.08)	0.16	12.06 (0.02)	67
	Second or later born	5	769	0.88 (0.69–1.13)	0.33	16.82 (0.002)	76
In case–control studies (adjusted for maternal age[a])	First born		1002	1.00 (Ref. Cat.)			
	Second born	19	608	0.87 (0.76–0.99)	0.03	10.95 (0.90)	0
	Third or later born	19	269	0.74 (0.63–0.87)	<0.001	13.97 (0.73)	0
	Second or later born	20	916	0.81 (0.72–0.92)	0.001	11.65 (0.90)	0
In studies with a low risk of bias (adjusted for maternal age[a])	First born		627	1.00 (Ref. Cat.)			
	Second born	9	494	0.83 (0.67–1.03)	0.13	16.90 (0.03)	53
	Third or later born	9	320	0.73 (0.57–0.94)	0.02	16.15 (0.04)	50
	Second or later born	9	814	0.77 (0.62–0.97)	0.03	21.74 (0.005)	63

[a]Except for two studies where unadjusted estimates were used.[25,31]

Discussion

This pooled analysis shows that second- or later born children experience a reduction in type 1 diabetes risk of ~10%, but this association varied between studies. The association was only apparent after adjustment for maternal age at birth, perhaps because first-born children have younger mothers and are consequently at reduced diabetes risk.[4] An a priori subgroup analysis demonstrated a stronger and more consistent association in children aged <5 years.

This is, to our knowledge, the first systematic review and pooled analysis of the association between birth order and the risk of type 1 diabetes. The main strength of this review is that it contains data from up to 11 955 cases from up to 31 studies with consistent categorization of study variables and adjustment for relevant potential confounders. As with all meta-analyses, it is possible that publication bias could have led to the exaggeration of the observed effects but there was little evidence of any such bias from funnel plots. Of the four studies that were identified by literature searches but could not be included, one reported a reduced risk of diabetes in fifth- or later born children,[14] two reported no association between birth order and diabetes[15,22] and one did not report any data on the association.[28] Birth order may have been reported differently between studies for a small minority of children (such as those born following still births, twins or adopted siblings) but it seems unlikely that such variations could bias results.

The cause of any increase in the risk of childhood type 1 diabetes in first born children is unknown. It is possible to speculate that prenatal exposures which depend upon the mother's parity may be involved, such as maternal immune response.[39] Alternatively, birth order may be a marker of postnatal exposures as it is likely that first-born children have a reduced or delayed exposure to infections such as enteroviruses,[40] assuming that later born children share the household with older siblings who are exposed to infectious agents at school or day care. So, this finding may provide indirect support for the hygiene hypothesis, which suggests that the immune system requires stimulation by infections and other immune challenges in early life to achieve a mature and balanced repertoire of responses.[3] Weak support for this theory has come from animal models of infection in the non-obese diabetic (NOD) mouse, which have shown that infections can both reduce and increase diabetes risk.[41] Various markers for infection have been used in epidemiological investigations. These studies have shown some evidence of a reduction in

the risk of diabetes in children attending day care,[42,43] providing some support for the hygiene hypothesis. Conversely, studies of the association between childhood diabetes and infections in early life, whether recorded by maternal recall[43–45] or routinely recorded[46–48] (in hospital or general practice), have reached inconsistent conclusions.

Any increase in childhood diabetes risk in first-born children may have alternative explanations as parents may do many things differently for their first child compared with subsequent children. A strength of our analysis was the ability to adjust for some of these differences. Our analysis shows that the observed association between diabetes and birth order could not be explained by differences in breastfeeding practices or caesarean section delivery rates between first- and later born children. However, there may be differences that were not recorded, but it is difficult to propose plausible candidates as few environmental factors have yet been established as risk factors for type 1 diabetes.[3]

In conclusion, there is some evidence of a relationship between increasing birth order and lower risk of type 1 diabetes in children, particularly among children aged <5 years.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- In 31 observational studies (including 11 955 cases), children who were second or higher in birth order had a reduced risk of childhood diabetes by, on average, 10% (after adjusting for other confounders) but this association varied markedly between studies. This association was stronger and more consistent in children <5 years of age.
- The cause of any reduction in diabetes risk in children of higher birth order is unknown, but could reflect increased exposure to sibling infections early in life.

References

[1] The DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes worldwide 1990–1999. *Diabet Med* 2006;**23:**857–66.

[2] Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. the EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005–20: a multicentre prospective registration study. *Lancet* 2009;**373:** 2027–33.

[3] Gale EA. A missing link in the hygiene hypothesis? *Diabetologia* 2002;**45:**588–94.

[4] Cardwell CR, Stene LC, Joner G *et al*. Maternal age at birth and childhood type 1 diabetes: a pooled analysis of 30 observational studies. *Diabetes* 2010;**59:**486–94.

[5] Stene LC, Magnus P, Lie RT, Sovik O, Joner G. Maternal and paternal age at delivery, birth order, and risk of childhood onset type 1 diabetes: population based cohort study. *BMJ* 2001;**323:**369.

[6] Dahlquist G, Patterson C, Soltesz G. Perinatal risk factors for childhood type 1 diabetes in Europe. The EURODIAB Substudy 2 Study Group. *Diabetes Care* 1999;**22:**1698–702.

[7] Sadauskaite-Kuehne V, Ludvigsson J, Padaiga Z, Jasinskiene E, Samuelsson U. Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. *Diabetes Metab Res Rev* 2004;**20:**150–57.

[8] Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. *Stat Med* 2001;**20:**2115–30.

[9] Kirkwood BR, Sterne JAC. *Essential Medical Statistics*. Oxford: Blackwell Science Ltd, 2003.

[10] Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. *Methods for Meta-Analysis in Medical Research*. Chichester: John Wiley & Sons Ltd, 2000.

[11] Cardwell CR, Carson DJ, Patterson CC. Parental age at delivery, birth order, birth weight and gestational age are associated with the risk of childhood type 1 diabetes: a UK regional retrospective cohort study. *Diabet Med* 2005; **22:**200–06.

[12] Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;**326:**219.

[13] Glatthaar C, Whittall DE, Welborn TA *et al*. Diabetes in Western Australian children: descriptive epidemiology. *Med J Aust* 1988;**148:**117–23.

[14] Virtanen SM, Rasanen L, Ylonen K *et al*. Early introduction of dairy products associated with increased risk of IDDM in Finnish children. Childhood Diabetes in Finland Study Group. *Diabetes* 1993;**42:**1786–90.

[15] Lawler-Heavner J, Cruickshanks KJ, Hay WW, Gay EC, Hamman RF. Birth size and risk of insulin-dependent diabetes-mellitus (IDDM). *Diabetes Res Clin Pract* 1994; **24:**153–59.

[16] Patterson CC, Carson DJ, Hadden DR, Waugh NR, Cole SK. A case-control investigation of perinatal risk factors for childhood IDDM in Northern Ireland and Scotland. *Diabetes Care* 1994;**17:**376–81.

[17] Bock T, Pedersen CR, Volund A, Pallesen CS, Buschard K. Perinatal determinants among children who later develop IDDM. *Diabetes Care* 1994;**17:**1154–57.

[18] Wadsworth EJK, Shield JPH, Hunt LP, Baum JD. A case-control study of environmental factors associated with diabetes in the under 5s. *Diabet Med* 1997;**14:**390–96.

[19] Gimeno SG, de Souza JM. IDDM and milk consumption. A case-control study in Sao Paulo, Brazil. *Diabetes Care* 1997;**20:**1256–60.

[20] McKinney PA, Parslow R, Gurney KA, Law GR, Bodansky HJ, Williams R. Perinatal and neonatal determinants of childhood type 1 diabetes. A case-control study in Yorkshire, U.K. *Diabetes Care* 1999;**22:**928–32.

[21] Rami B, Schneider U, Imhof A, Waldhor T, Schober E. Risk factors for type I diabetes mellitus in children in Austria. *Eur J Pediatr* 1999;**158:**362–66.

[22] Bache I, Bock T, Volund A, Buschard K. Previous maternal abortion, longer gestation, and younger maternal age decrease the risk of type 1 diabetes among male offspring. *Diabetes Care* 1999;**22:**1063–65.

[23] Stene LC, Joner G. The Norwegian Childhood Diabetes Study Group. Atopic disorders and risk of childhood-onset type 1 diabetes in individuals. *Clin Exp Allergy* 2004;**34:**201–6.

[24] Sumnik Z, Drevinek P, Lanska V, Malcova H, Vavrinec J, Cinek O. Higher maternal age at delivery, and lower birth orders are associated with increased risk of childhood type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2004;**112:**294–97.

[25] Marshall AL, Chetwynd A, Morris JA *et al*. Type 1 diabetes mellitus in childhood: a matched case control study in Lancashire and Cumbria, UK. *Diabet Med* 2004; **21:**1035–40.

[26] Sipetic SB, Vlajinac HD, Kocev NI, Marinkovic JM, Radmanovic SZ, Bjekic MD. The Belgrade childhood diabetes study: a multivariate analysis of risk determinants for diabetes. *Eur J Public Health* 2005;**15:** 117–22.

[27] Svensson J, Carstensen B, Mortensen HB, Borch-Johnsen K. Early childhood risk factors associated with type 1 diabetes–is gender important? *Eur J Epidemiol* 2005;**20:**429–34.

[28] Dahlquist GG, Pundziute-Lycka A, Nystrom L. Birthweight and risk of type 1 diabetes in children and young adults: a population-based register study. *Diabetologia* 2005;**48:**1114–17.

[29] Bottini N, Meloni GF, Lucarelli P *et al*. Risk of type 1 diabetes in childhood and maternal age at delivery, interaction with ACP1 and sex. *Diabetes Metab Res Rev* 2005;**21:** 353–58.

[30] Radon K, Windstetter D, Solfrank S, von Mutius E, Nowak D, Schwarz HP. Exposure to farming environments in early life and type 1 diabetes: a case-control study. *Diabetes* 2005;**54:**3212–16.

[31] Polanska J, Jarosz-Chobot P. Maternal age at delivery and order of birth are risk factors for type 1 diabetes mellitus in Upper Silesia, Poland. *Med Sci Monit* 2006;**12:** CR173–76.

[32] Wei JN, Li HY, Chang CH *et al*. Birth weight and type 1 diabetes among schoolchildren in Taiwan–A population-based case-controlled study. *Diabetes Res Clin Pract* 2006; **74:**309–15.

[33] Tenconi MT, Devoti G, Comelli M *et al*. Major childhood infectious diseases and other determinants associated with type 1 diabetes: a case-control study. *Acta Diabetol* 2007;**44:**14–19.

[34] Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA. Perinatal risk factors for childhood Type 1 diabetes in Western Australia–a population-based study (1980–2002). *Diabet Med* 2007;**24:**564–70.

[35] Ievins R, Roberts SE, Goldacre MJ. Perinatal factors associated with subsequent diabetes mellitus in the child: record linkage study. *Diabet Med* 2007;**24:**664–70.

[36] Rosenbauer J, Herzig P, Giani G. Early infant feeding and risk of type 1 diabetes mellitus-a nationwide population-based case-control study in pre-school children. *Diabetes Metab Res Rev* 2008;**24:**211–22.

[37] Waldhoer T, Rami B, Schober E. Perinatal risk factors for early childhood onset type 1 diabetes in Austria - a population-based study (1989–2005). *Pediatr Diabetes* 2008;**9:**178–81.

[38] Algert CS, McElduff A, Morris JM, Roberts CL. Perinatal risk factors for early onset of Type 1 diabetes in a 2000-2005 birth cohort. *Diabet Med* 2009;**26:**1193–97.

[39] Karmaus W, Johnson CC. Invited commentary: Sibship effects and a call for a comparative disease approach. *Am J Epidemiol* 2005;**162:**133–38.

[40] Witso E, Cinek O, Aldrin M *et al*. Predictors of sub-clinical enterovirus infections in infants: a prospective cohort study. *Int J Epidemiol* 2009;**39:**459–68.

[41] Filippi CM, Estes EA, Oldham JE, von Herrath MG. Immunoregulatory mechanisms triggered by viral infections protect from type 1 diabetes in mice. *J Clin Invest* 2009;**119:**1515–23.

[42] Kaila B, Taback SP. The effect of day care exposure on the risk of developing type 1 diabetes: a meta-analysis of case-control studies. *Diabetes Care* 2001;**24:**1353–58.

[43] The EURODIAB Substudy 2 Study Group. Infections and vaccinations as risk factors for childhood type I (insulin-dependent) diabetes mellitus: a multicentre case-control investigation. *Diabetologia* 2000;**43:**47–53.

[44] Soltesz G, Jeges S, Dahlquist G *et al*. Nongenetic Risk Determinants for Type-I (Insulin-Dependent) Diabetes-Mellitus in Childhood. *Acta Paediatrica* 1994;**83:** 730–35.

[45] Blom L, Nystrom L, Dahlquist G. The Swedish childhood diabetes study – vaccinations and infections as risk determinants for diabetes in childhood. *Diabetologia* 1991;**34:** 176–81.

[46] Pundziute-Lycka A, Urbonaite B, Dahlquist G. Infections and risk of Type I (insulin-dependent) diabetes mellitus in Lithuanian children. *Diabetologia* 2000;**43:** 1229–34.

[47] Gibbon C, Smith T, Egger P, Betts P, Phillips D. Early infection and subsequent insulin dependent diabetes. *Arch Dis Child* 1997;**77:**384–85.

[48] Cardwell CR, Carson DJ, Patterson CC. No association between routinely recorded infections in early life and subsequent risk of childhood-onset Type 1 diabetes: a matched case-control study using the UK General Practice Research Database. *Diabet Med* 2008;**25:**261–67.